APPEAL BRIEF

Peter I. Bernstein
Attorney for Appellants
Registration No. 43,497

Scully, Scott, Murphy & Presser, P.C.
400 Garden City Plaza, Suite 300
Garden City, New York 11530
(516) 742-4343

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Maria Adele Pacciarini
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Docket:	17815
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Art Unit:	1623
Confirmation No.:	1122
Dated:	May 6, 2013
For:	USE OF METHOXYMORPHOLINO DOXORUBICIN FOR THE TREATMENT OF A LIVER TUMOR

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Pursuant to 35 U.S.C. §134 and 37 C.F.R. §41.37, entry of this Appeal Brief, related to the Notice of Appeal filed March 5, 2013 in the above application, is respectfully requested. This Brief sets forth the authorities and arguments upon which Appellants rely in support of the Official Action dated December 5, 2012, which rejected Claims 18, 20-23, 26, 27, 29, 30, 34-42. These claims have been at least twice rejected, i.e. Official Action of January 9, 2012, Official Action of December 5, 2012. This appeal is therefore proper.

CERTIFICATE OF ELECTRONIC FILING

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Dated: May 6, 2013

/Peter I. Bernstein/
Peter I. Bernstein

I. Real Party in Interest

The real party in interest is Neviano Medical Sciences S.r.l.

II. Related Appeals and Interferences

This application was previously appealed to the Board of Patent Appeals and Interferences as Appeal No. 2008-5301, decided February 25, 2009. A copy of the decision is included in the Related Proceedings Appendix annexed hereto as required by 37 C.F.R. 41.37.

No other prior or pending appeals, interferences or judicial proceedings are known to Appellants or their legal representative or assignee which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in this pending appeal.

III. Status of Claims

Claims 1-17 have been cancelled.

Claim 18 is twice rejected.

Claim 19 has been cancelled.

Claims 20-23 have been twice rejected.

Claims 24-25 have been cancelled.

Claims 26-27 have been twice rejected.

Claim 28 has been cancelled.

Claims 29-30 have been twice rejected.

Claims 31-33 have been cancelled.

Claims 43-42 have been twice rejected.

IV. Status of Amendments

No amendments to the claims have been filed after the Official Actions of January 9, 2012 and December 5, 2012 which twice rejected the claims.

V. Summary of Claimed Subject Matter

The application presently contains three independent claims: Claims 18, 34, and 40. All are on appeal, as well as their independent claims. They are summarized as follows:

Claims 18 and 40 are to a method of treating human liver cancer. A feature common to all method claims is the intrahepatic administration of MMDX, in a therapeutic amount. Depending on the claim, the MMDX is administered as an infusion from about 15 minutes to about 30 minutes every 4 weeks, or as a 5-10 minute bolus every 8 weeks.

Claim 34 is a pharmaceutical composition for the treatment of a human liver cancer by intrahepatic administration via injection into the hepatic artery. The composition comprises MMDX in an amount sufficient to provide a dosage of about 100 mcg/m2 to about 1000 mcg/m2; and a pharmaceutically acceptable agent which remains selectively in a liver tumor after injection, *e.g.* an iodized oil.

Claims 18, 34 and 42 are hereinbelow mapped in accordance with 37 CFR 41.37 with specification and line numbers for the elements claimed are interposed in **[boldface]:**

18. A method of treating a human liver cancer which comprises the intrahepatic administration of a therapeutically effective amount of methoxymorpholino doxorubicin (MMDX) to a patient in need thereof **[see e.g. page 7, line, 30 to page 8, line 13]** wherein said MMDX is administered in a dose ranging from about 100 mcg/m^2 to about 1000 mcg/m^2**[see e.g. page 8, lines 25-29]**.

34. A pharmaceutical composition for the treatment of a human liver cancer by intrahepatic administration via injection into the hepatic artery **[see e.g. page 10, lines 17-23]** comprising: a) methoxymorpholino doxorubicin (MMDX) in an amount sufficient to provide a dosage of about 100 mcg/m^2 to about 1000 mcg/m^2 **[see e.g. page 8, lines 25-29]**; and b) a pharmaceutically acceptable agent which remains selectively in a liver tumor after its injection into the hepatic artery **[see page 10, lines 19-21]**.

40. A method of treating a human liver cancer wherein the liver cancer is a tumor primarily confined to the liver and is selected from hepatocellular carcinoma (HCC) or a cholangiocarcinoma, or wherein said liver cancer is a liver metastasis **[see e.g. page 8, lines 8-11]**, comprising the intrahepatic administration to a patient in need thereof, via the hepatic artery, of a therapeutically effective amount of methoxymorpholino doxorubicin (MMDX) **[see e.g. page 7 line 30 to page 8 line 13]** with iodized oil **[see e.g. page 9, line 3]**, wherein said MMDX is administered as an infusion of from about 15 minutes to about 30 minutes every 4 weeks **[see e.g. page 8, lines 14-17]** in a dose ranging from about 100 mcg/m^2 to about 1000 mcg/m^2 **[see e.g. page 8, lines 25-29]**.

VI. Grounds of Rejection to be Reviewed on Appeal

There is a single ground for rejection: all claims on appeal—Claims 18, 20-23, 26, 27, 29, 30, and 34-42— are rejected as obvious under 35 USC §103 citing US Patent No. 5304687 to Bargiotti et al. ("Bargiotti") in view of Kuhl et el., *Cancer Chemother. Pharmacol.*, 1993, 33, 10-16 ("Kuhl") in view of Nakamura et al., *Gan. To Kagaku Ryoho* 1988, Aug. 15 (8 Pt 2), 2562-7, English Abstract) ("Nakamura") and further in view of Gorbunova, *Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver*, 1990 ("Gorbunova") and US Patent No. 5626862 to Brem et al. ("Brem").

Prior art submitted during prosecution by Appellants, which art is of record and relied upon herein for purposes of rebuttal in this appeal, include:

- Hamamoto et al. "Microsomal Cyctochrome P-450-linked Monooxygenase Systems and Lipid Composition of Human Hepatocelluar Carcinoma" *British Journal of Cancer*, 59(1) pp. 6-11 (1989) ("Hamamoto");

- Omura et al. "The Carbon Monooxide-binding Pigment of Liver Microsomes" *Journal of Biological Chemistry*, vol. 34, No.7, July 1964, pp. 2370-2378 ("Omura");

- Eriksson et al. "Distinctive Biochemical Pattern Associated with Resistance of Hepatocytes in Hepatocyte Nodules during Liver Carcinogenesis" *Environmental Health Perspectives*, Vol. 49, pp. 171-174 (1983) ("Eriksson"); and

- El Mouelhi et al. "Hepatic Drug-metabolizing enzymes in Primary and Secondary Tumors of Human Liver" *Cancer Research*, 47, pp. 460-466 (1987) ("El Mouelhi").

VII. Arguments

A.) Background

Commonly, the aforesaid claims are to a method of treating human liver cancer (Claims 18 and 42), and to a pharmaceutical composition for such treatment (Claim 34). The active ingredient is methoxymorpholino doxorubicin (MMDX). The mode of administration is via intrahepatic administration.

Of the five references cited to support the obviousness rejection, none disclose MMDX for treating liver cancer, or indeed for any liver affliction. Indeed, only two of the references discuss MMDX at all: Bargiotti et al. discloses a belief that MMDX has solid antitumor activity but discloses data only for human mammary carcinoma. Kuhl et al. mentions MMDX as having broad spectrum antitumor activity and relates information on MMDX only in human leukemia and human lymphoma cell lines. Again, liver cancer is undisclosed. To remedy this failing, the rejection imports Nakumura.

Nakumura teaches treatment of certain liver cancers using another compound, adriamycin, also known as doxorubicin, ("ADM"). MMDX is not ADM. Gorbunova is supplied for its teaching of intrahepatic arterial infusion in certain heptic carcinoma. Among the actives is ADM. Brem is offered for its alleged teachings of pulse and short term administrations, see e.g. Claim 42.

The rejection posits that one in the art would have been motivated to swap the MMDX of Bargiotti and Kuhl for the ADM in liver cancer treatments disclosed by Nakumura and Gorbunova, and that the claims thus would have been obvious, including the particular protocols claimed, for which Brem is provided.

Relatedly, the expectation for success in making this switch, as legally required under 35 USC §103, is alleged to be the potentiation of MMDX in the liver. Ordinarily, MMDX produces a high concentration of metabolite in the liver, see e.g. the Official Action of December 5, 2012, page 9, second full paragraph (in that portion of the Official Action sylted "Response to Applicants Arguments") discussing Kuhl, the abstract for which purports to teach that this MMDX liver metabolite crosslinks to DNA and is ten times (10x) more potent than MMDX; and Gorbunova, which avers concentration advantages in certain instances for intrahepatic arterial administration. This conclusion, however, hinges on the presupposition that the liver in question is a healthy liver.

Critically, the instant claims do not concern a healthy liver. They are, instead, by their own words, directed to a cancerous liver. Thus any alleged potentiation of MMDX by the liver must take into account the adverse effect on same when the liver is diseased. As discussed below, at the time of filing for this application, it was known that when the liver itself was cancerous — which, again, is the subject matter of the instant claims— the liver microsome principally involved in drug metabolism was severely depleted and/or converted to inactive forms.

It is Appellants' position that this circumstance undermines any alleged reasonable expectation of success in using MMDX; that the legal analysis underlying the obviousness rejection failed to adequately consider this; that this is error; and that the claims are non-obvious and should be passed to allowance.

B.) Lack of Reasonable Expectation of Success

Case law requires that for a rejection under §103 to be tenable in the first instance, the skilled artisan must have a reasonable expectation that the proposed combination or modification of prior art teachings would be successful. As articulated by the Federal Circuit in *Medichem S.A. v. Rolabo S.L.*, 77 USPQ2d 1865, 1870 (2006) (emphasis in original):

> "…an obviousness determination requires not only the existence of a motivation to combine elements from different prior art references, but also that a skilled artisan would have perceived a reasonable expectation of success in making the invention via that combination. While the definition of "reasonable expectation" is somewhat vague, our case law makes clear that it does not require a *certainty* of success. *See In re O'Farrell*, 853 F.2d 894, 903-04 [7 USPQ2d 1673] (Fed. Cir. 1988) ("Obviousness does not require absolute predictability of success.... [A]ll that is required is a reasonable expectation of success.")."

Medichem, ibid, also admonishes that as part of the assessment:

> "Where the prior art contains 'apparently conflicting' teachings (i.e. where some references teach the combination and others teach away from it) each reference must be considered 'for its power to suggest solutions to an artisan or ordinary skill…consider[ing] the degree to which one reference might accurately discredit another.' *In re Young*, 927 F.2d 588, 591 [18 USPQ2d 1089] (Fed. Cir. 1991)."

See also, *DePuy Spine Inc. v. Medtronic Sofamor Danek*, 90 USPQ2d 1865, 1873 (Fed. Cir. 2009):

> "The opposite conclusion [i.e. a conclusion of non-obviousness] would follow, however, if the prior art indicated that the invention would not have worked for its intended purpose or otherwise taught away from the invention. *See United States v. Adams*, 383 U.S. 39, 52 (1966) (upholding nonobviousness where references teaching away from the claimed combination would "deter any investigation into such a combination"); *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1382 [83 USPQ2d 1746] (Fed. Cir. 2007) ("[A] reference teaches away from a combination when using it in that combination would produce an inoperative result."). An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements."

Here, the rejection posits that because the prior art of Kuhl describes a ten-fold activation in the liver for MMDX metabolites, there is a reasonable expectation of success of using MMDX in lieu of ADM. Discrediting this is art submitted by Applicant (now Appellant) that a cancerous liver would <u>not</u> function in the manner postulated, and that one would <u>not</u> have a reasonable expectation of successful potentiation.

Thus, when this application was filed, it was known that the liver microsome designated as P-450 was the microsome principally involved in drug metabolism. The artisan also knew then that when the liver itself was cancerous, this microsome, as well as other such components, was adversely affected. See e.g., Hamamoto et al. "Microsomal Cyctochrome P-450-linked Monooxygenase Systems and Lipid Composition of Human Hepatocelluar Carcinoma" *British Journal of Cancer*, 59(1) pp. 6-11 (1989), the abstract of which clearly teaches:

> "In microsomes of hepatocelluar carcinoma tissues, there was as much cyctochrome P-450 and other redox components as in the normal liver tissues, but cytochrome P-450 in liver cancer tissues was unstable and easily converted to cytochrome P-420. The specific activities of NADPH- and NADH-ferricyanide and cytochrome c reductase of each sample were also measured. In the microsomes of the cancer tissues, the specific activities were remarkably reduced compared with those of normal liver tissues."

On top of this, the artisan also knew that cytochrome P-420 —that is, the cytochrome into which P-450 is "easily converted" in cancerous liver tissue— is an inactive form, see e.g. Omura et al. "The Carbon Monooxide-binding Pigment of Liver Microsomes" *Journal of Biological Chemistry*, vol. 34, No.7, July 1964, pp. 2370-2378. See also in this regard, Eriksson et al. "Distinctive Biochemical Pattern Associated with Resistance of Hepatocytes in Hepatocyte Nodules during Liver Carcinogenesis" *Environmental Health Perspectives*, Vol. 49, pp. 171-174 (1983); and El Mouelhi et al. "Hepatic Drug-metabolizing enzymes in Primary and Secondary Tumors of Human Liver" *Cancer Research*, 47, pp. 460-466 (1987) which indicate that drug-metabolizing liver enzymes are markedly decreased in cancerous livers.

Court decisions with not dissimilar facts as here, have ruled in favor of non-obviousness. See e.g. *Eli Lilly and Co. v. Teva Pharmaceuticals*, 96 USPQ2d 1375 (Fed. Cir. 2010). There, the claims were directed to treatment of osteoporosis using a known compound (raloxifene). The prior art, however, taught poor bioavailability for raloxifene. In finding the claims patentable, the Federal Circuit approvingly noted the District Court finding that:

> "...the widely reported bioavailability concerns would have precluded a person of ordinary skill in the art from reasonably expecting to successfully treat postmenopausal osteoporosis with raloxifene."

56 USPQ2d at 1381.

And further found there was;

> "...no evidence from before the time of invention that would teach, suggest, or motivate or supply any common sense reason for a person of ordinary skill in the art to reject the bioavailability concerns and...one of skill in the art would have been dissuaded from using raloxifene to treat postmenopausal osteoporosis in light of published bioavailability data."

56 USPQ2d at 1382.

See also *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 102 USPQ2d 1760 (Fed. Cir. 2012) wherein the lower court's finding of obviousness was reversed, the Federal Circuit observing:

> "While it may have been obvious to experiment with the use of the same PK [pharmacokinetic] profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective. *See Proctor & Gamble,* 566 F.3d at 994 (requiring a reasonable expectation of success to prove obviousness)."

In the instant situation, the notion that one would be motivated by successful expectation that MMDX would be potentiated in the liver is discredited by countervailing art establishing that in a cancerous liver, the drug metabolizing microsomes that would potentiate are instead compromised.

The Official Action of December 5, 2012 responds (page 9, last full paragraph bridging to page 10) by arguing that even though MMDX is not potentiated tenfold, as in a healthy liver:

> "...one of ordinary skill in the art will recognize that the lower amount of cyctochrome P-450 present in a cancerous liver can still metabolize MMDX. Even though the concentration of the metabolite will be lower, because it is ten times more potent it can still express its anticancer activity in the liver. It would be a problem only if cyctochrome P-450 is totally absent. According to Hammamo et al. it is not complete converted to P-420."

This conclusion is defective on several levels.

1) There is nothing of record to support the conclusion that there is some "lower" remaining level of metabolite provided by a cancerous liver sufficient to uphold a reasonable expectation of successful MMDX potentiation. It is, therefore, nothing more than an *ipse dixit* statement, to be entirely discounted as mere speculation. Moreover, the conclusion begs the question. It starts with a tenfold potentiation in the liver, lowered thereafter to account for liver cancer. But the art provided by Appellants in rebuttal shows that a cancerous liver does not function as a normal one. There is thus no reason to presume a tenfold potentiation, or any multiple of potentiation, in the first instance, hence no reason to presume what, if any, level of potentiate remains.

2) The conclusion that P-450 must be "totally absent" in order to discredit the expectation of success is, on its face, fatally erroneous, and is a distortion of Appellants' position. Just as obviousness does not require absolute predictability of success, neither does non-obviousness require absolute predictability of failure. The question is not posed in absolutes. It turns on the presence or absence of a reasonable expectation of success. See e.g. *Rolabo S.L. supra.* Here, the rejection is premised on potentiation of MMDX into a more active metabolite. Appellants have countered with art showing such potentiation was indeed seriously compromised in a cancerous liver. What would have been expected, therefore, is thrown into doubt to such an extent that it is removed from the realm of what is reasonable.

Importantly, Appellants note in this regard the Patent Office's own guidelines, *Patent Examination Policy - MPEP Staff - 35 U.S.C. § 112 1st para - Enablement of Chemical/Biotechnical Applications* which states repeatedly that the cancer therapy art remains "highly unpredictable" see e.g. the Situations offered under Example F. Thus, the overarching unpredictability of the art in the first instance, when applied to an expectation of success, whose predictability is then further unsettled by Appellants' submissions on potentiation in a cancerous liver, is submitted to be more than enough to obviate the rejection. Perfect failure, i.e. a showing of total absence of potentiation, is unneeded and not the law.

3) This conclusion improperly changes the rejection in a material way. That is, the rejection as originally applied relied on a tenfold potentiation of MMDX. Now, something less than this multiple, which is not even quantified, is relied upon for the rejection. At the very least, this is a concession to Appellants' position that potentiation is very much adversely affected, and that what was an alleged reasonable expectation of success has been dramatically shaken.

Applicants submit that the potentiation of MMDX in a cancerous liver is thrown into issue and doubt sufficient to eliminate any reasonable expectation that it would occur successfully as officially postulated. Applicants further submit that this, in conjunction with the unpredictability of this art, as recognized by the Patent Office itself, is enough to remove the rejection and find the claims non-obvious.

C.) Claim 40

Appellants hereby argue the separate patentability of independent Claim 40 (and necessarily, by dependency, Claims 41-42.)

The foregoing argument applies to independent Claim 40, in full. That is, the liver potentiation relied upon for the rejection is usurped when the liver itself is cancer stricken. Any expectation that such would occur in the manner proposed by the rejection is less than reasonable and is too unpredictable.

While this alone merits a finding of non-obviousness, Claim 40 further specifies the liver cancer treated as hepatocellular carcinoma (HCC) or a cholangiocarcinoma, and dictates the dosage regimen for MMDX as an infusion, via hepatic artery, with iodised oil, of from about 15 minutes to about 30 minutes every 4 weeks in a dose ranging from about 100 mcg/m^2 to about 1000 mcg/m^2. None of the references fairly suggest this particular protocol for MMDX. Indeed, the data in the instant application shows a dramatic and unexpected reduction in side effects, such as hematological and non-hematological toxicity associated with this method. For example, at page 11, line 27 to page 12, line 3, the instant specification reports on hematological toxicity in clinical studies performed with the invention. By way of example, it is reported that Grade 1 leucopenia was observed with the practice of the invention at dosage levels claimed. Grade 1 is

understood by the artisan to be the mildest grade measure for toxic effect of chemotherapy. Moreover, the specification further relates that even non-hematological toxicity (at page 12) was generally only mild to moderate, i.e. was generally Grade 1 or 2, which grades are again indicative of the low end of toxicity.

These advantages were not foreseen by the art of record. Indeed, as already noted, the art cited either makes no mention of MMDX in the context of human liver cancer, including especially that select parameters of dosage level and administration route as per Claim 40 would produce a tremendous lessening of deleterious side effects. This, alone or in conjunction with the lack of reasonable expectation of successful potentiation of MMDX as before stated clearly bespeaks the non-obviousness of Claim 40 and its dependencies, Claims 41 and 42.

VIII. Conclusion

The rejection of Claims 18, 20-23, 26, 27, 29, 30, 34-42 under 35 USC §103 should be withdrawn for the before stated reasons.

WHEREFORE, it is believed the patentability of this application is established, a favorable decision on appeal is respectfully requested.

Respectfully submitted,

/Peter I. Bernstein/

Peter I. Bernstein
Registration No. 43,497

Scully, Scott, Murphy, & Presser, P.C.
400 Garden City Plaza, Suite 300
Garden City, New York 11530
516-742-4343
RLC/PIB:dk

IX. Claims Appendix

A copy of the claims on appeal, Claims 18, 20-23, 26, 27, 29, 30, 34-42, are annexed hereto at the Claims Appendix.

18. A method of treating a human liver cancer which comprises the intrahepatic administration of a therapeutically effective amount of methoxymorpholino doxorubicin (MMDX) to a patient in need thereof, wherein said MMDX is administered in a dose ranging from about 100 mcg/m^2 to about 1000 mcg/m^2.

20. The method according to claim 18, wherein the liver tumor is a tumor primarily confined to the liver.

21. The method according to claim 20, wherein the tumor primarily confined to the liver is a hepatocellular carcinoma (HCC) or a cholangiocarcinoma.

22. The method according to claim 18, wherein the tumor is a liver metastasis.

23. The method according to claim 18, wherein the intrahepatic administration of MMDX is via the hepatic artery.

26. The method according to claim 18, wherein MMDX is administered with an agent, which remains selectively in a liver tumor after its injection into the hepatic artery.

27. The method according to claim 26, wherein the agent is iodized oil.

29. The method according to claim 18, wherein MMDX is administered in a dose ranging from about 100 mcg/m^2 to about 800 mcg/m^2.

30. The method according to claim 29, wherein the dose is 200 mcg/m^2.

34. A pharmaceutical composition for the treatment of a human liver cancer by intrahepatic administration via injection into the hepatic artery comprising:

a) methoxymorpholino doxorubicin (MMDX) in an amount sufficient to provide a dosage of about 100 mcg/m^2 to about 1000 mcg/m^2; and

b) a pharmaceutically acceptable agent which remains selectively in a liver tumor after its injection into the hepatic artery.

35. The pharmaceutical composition of claim 34 wherein the MMDX is in an amount sufficient to provide a dosage of about 100mcg/m^2 to about 800 mcg/m^2.

36. The pharmaceutical composition of claim 34 wherein the MMDX is in an amount sufficient to provide a dosage of about 200mcg/m^2.

37. The pharmaceutical composition of claim 34 wherein the agent is iodized oil.

38. The method according to Claim 18 wherein the MMDX is further administered as an infusion of from about 15 minutes to about 30 minutes every 4 weeks.

39. The method according to Claim 18 wherein the MMDX is further administered as a 5-10 minute bolus every 8 weeks.

40. A method of treating a human liver cancer wherein the liver cancer is a tumor primarily confined to the liver and is selected from hepatocellular carcinoma (HCC) or a cholangiocarcinoma, or wherein said liver cancer is a liver metastasis, comprising the intrahepatic administration to a patient in need thereof, via the hepatic artery, of a therapeutically effective amount of methoxymorpholino doxorubicin (MMDX) with iodized oil, wherein said MMDX is administered as an infusion of from about 15 minutes to about 30 minutes every 4 weeks in a dose ranging from about 100 mcg/m^2 to about 1000 mcg/m^2.

41. The method according to Claim 40 wherein said MMDX is administered in a dose ranging from about 100 mcg/m^2 to about 800 mcg/m^2.

42. The method according to Claim 41 wherein said MMDX is administered in a dose of 200 mcg/m^2.

X. Evidence Appendix

No affidavits or declarations under 37 C.F.R. §§1.130, 1.131, or 1.132 have been submitted or are relied upon in this appeal.

XI. Related Proceeding Appendix

A copy of the Board of Patent Appeals decision in Appeal No. 2008-5301, decided February 25, 2009, is annexed in the Related Proceeding Index.

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PETER I. BERNSTEIN
BERNSTEIN, SCULLY, SCOTT, MURPHY & PRESSER
400 GARDEN CITY PLAZA
GARDEN CITY, NY 11530

EXAMINER	
KRISHNAN, GANAPATHY	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MARIA ADELE PACCIARINI, OLGA VALOTA, and DAVID KERR[1]

Appeal 2008-5301[2]
Application 09/786,998
Technology Center 1600

Decided:[3] February 25, 2009

Before DONALD E. ADAMS, LORA M. GREEN, and MELANIE L. McCOLLUM, *Administrative Patent Judges.*

McCOLLUM, *Administrative Patent Judge.*

DECISION ON APPEAL

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[1] The real party in interest is Nerviano Medical Sciences S.r.l. (App. Br. 2).
[2] Oral Hearing held February 3, 2009.
[3] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

This is an appeal under 35 U.S.C. § 134 involving claims to a pharmaceutical composition and a treatment method. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

Claims 13, 14, and 18-31 are pending and on appeal. We will focus on claims 13, 18, 19, 24, 25, 28, and 31, which read as follows:

13. A pharmaceutical composition which comprises as an active principle MMDX and a pharmaceutically acceptable agent which remains selectively in a liver tumor after its injection through the hepatic artery.

18. A method of treating a human liver tumor which comprises the intrahepatic administration of a therapeutically effective amount of methoxymorpholino doxorubicin (MMDX) to a patient in need thereof.

19. A method for reducing methoxymorpholino doxorubicin systemic exposure of a patient suffering from a liver cancer which comprises the intrahepatic administration of a therapeutically effective amount of methoxymorpholino doxorubicin (MMDX) to said patient.

24. A method according to claim 18, wherein MMDX is administered as an infusion of from about 15 minutes to about 30 minutes every 4 weeks.

25. A method according to claim 18, wherein MMDX is administered as a 5-10 minute bolus every 8 weeks.

28. A method according to claim 1, wherein MMDX is administered in a dose ranging from about 100 mcg/m^2 to about 1000 mcg/m^2.

31. A method of treating human liver tumor, which comprises the intrahepatic administration of a therapeutically effective amount of a pharmaceutical composition which comprises as an active principle methoxymorpholino doxorubicin (MMDX) and a pharmaceutically acceptable agent which remains selectively in a liver tumor after its injection through the hepatic artery.

The Examiner relies on the following references:

Bargiotti et al., US 5,304,687, Apr. 19, 1994 (hereinafter "Bargiotti");

Jörn-Sven Kühl et al., *Effects of the methoxymorpholino derivative of doxorubicin and its bioactivated form versus doxorubicin on human leukemia and lymphoma cell lines and normal bone marrow*, 33 CANCER CHEMOTHER. PHARMACOL. 10-16 (1993) (hereinafter "Kuhl");

Y. Takayasu et al., *Large-dose intra-arterial injection of lipiodol in liver cancer*, 15 GAN TO KAGAKU RYOHO 2562-67 (1988) (for consistency with the Examiner and Appellants, hereinafter "Nakamura"); and

V.A. Gorbunova, *Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver*, 12 SOV. MED. 66-68 (1990) (hereinafter "Gorbunova").

Appellants rely on the following reference:

Edward Chu and Vincent T. DeVita, Jr., *Principles of Cancer Management: Chemotherapy*, in CANCER: PRINCIPLE AND PRACTICE OF ONCOLOGY 289-306 (Ch. 17) (hereinafter "DeVita").

Claims 13, 14, and 18-31 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Bargiotti, Kuhl, Nakamura, and Gorbunova (Ans. 3).

The Examiner relies on Bargiotti for teaching "morpholino derivatives of anthracyclines [including] methoxy morpholino doxorubicin" and that these "derivatives are shown to inhibit solid tumors such as human carcinoma with intravenous and oral route" (*id.*).

The Examiner relies on Kuhl for teaching "that the methoxymorpholino derivative of doxorubicin has a broad-spectrum

antitumor activity and is . . . activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent" (*id.* at 3-4.)

The Examiner relies on Nakamura for teaching that "intra-arterial infusion of lipiodol (iodized oil) and adriamycin (same as doxorubicin) showed remarkable therapeutic effects for advanced cancer" (*id.* at 4).

The Examiner relies on Gorbunova for teaching that "intra hepatic arterial infusion chemotherapy allows for creating a super high concentration of an antitumor agent in the organ affected by the tumor" (*id.*).

The Examiner concludes that it would have been obvious "to make a composition comprising methoxymorpholino doxorubicin [MMDX] with iodized oil and use the same in a method of treating a human liver tumor and reducing systemic exposure as instantly claimed" (*id.*). In particular, the Examiner argues that it "is logical that lipiodol (iodized oil) be administered in combination with MMDX since it has shown therapeutic effects when administered with the closely related adriamycin (adriamycin is the Trade name for doxorubicin and structurally very close to MMDX)" (*id.* at 4-5). In addition, the Examiner concludes that it "is well within the purview of one of ordinary skill in the art to adjust dosages and the frequency of administration based on that taught in the prior art" (*id.* at 4)

The Examiner also argues that "[o]ne of ordinary skill in the art would have been motivated to use MMDX . . . in hepatic artery administration since [the] prior art recognizes that hepatic artery administration of doxorubicin is beneficial in treating tumor" (*id.*). In addition, the Examiner argues that "[h]epatic arterial administration . . . creates super high concentrations in the organ affected" and this "localized administration is

beneficial for reducing systemic exposure and reducing tumor volume in the liver" (*id.*).

ISSUES

The issues on appeal are:

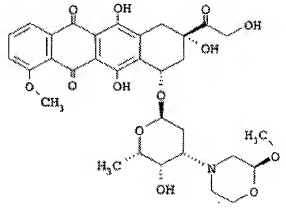
Did the Examiner set forth a prima facie case that: (a) it would have been obvious to combine MMDX with lipiodol; and (b) it would have been obvious to treat liver cancer by the intrahepatic administration of MMDX?

If so, did Appellants overcome the Examiner's prima facie case of obviousness with a showing of unexpected results?

FINDINGS OF FACT

1. The Specification discloses the "use of methoxymorpholino doxorubicin for the treatment of a liver cancer" (Spec. 1: 6-7).

2. "Methoxymorpholino doxorubicin (MMDX . . .) of formula



is a . . . doxorubicin derivative obtained with the substitution of the $-NH_2$ at position 3' in the sugar moiety with a methoxymorpholino group" (*id.* at 1: 11-16).

3. The Specification discloses that MMDX "differs from most anthracyclines in being highly potent when administered *in vivo*, the optimal i.v. dose being at least 80 fold less than that of doxorubicin" (*id.* at 2: 7-9).

4. The Specification also states:

> It would be . . . desirable to establish drug delivery strategies to avoid the high i.v. dosages of MMDX *presently believed to have an antitumor activity at the hepatic level* and to improve the antitumor efficacy of MMDX against a primary liver cancer and liver metastases.
>
> There is a need to achieve high MMDX concentration at the hepatic tumor site, while reducing systemic exposure and hence toxicity.
>
> The present invention fulfills such a need by providing a new method for administration of MMDX to a patient suffering from a liver tumor which reduces the MMDX amount without decreasing the MMDX's antitumor activity at the hepatic tumor site by directly injecting MMDX into the hepatic artery.

(*Id.* at 7: 13-25 (emphasis added).)

5. In addition, the Specification discloses mixing "the appropriate dose of MMDX . . . with a suitable amount of an agent which remains selectively in a liver tumor after its injection through the hepatic artery," such as iodized oil (LIPIODOL®) (*id.* at 8: 30 to 9: 9).

6. Bargiotti discloses anthracycline glycosides including MMDX in both the (S) and the (R) configurations (Bargiotti, col. 1, ll. 11-65).

7. Bargiotti states that the disclosed anthracycline glycosides are antitumor agents (*id.* at col. 5, ll. 27-30).

8. In particular, Bargiotti discloses that, in mice bearing Doxorubicin-resistant leukemia, (S)- and (R)-MMDX are "active and more potent that Doxorubicin" (*id.* at col. 11, ll. 42-61).

9. In addition, Bargiotti discloses that (S)-MMDX was shown to inhibit solid tumors, specifically murine and human mammary carcinomas (*id.* at col. 11, ll. 65-68, & col. 12, Tables 5-6).

10. Kuhl discloses that MMDX "has recently entered clinical trials because of its broad spectrum of preclinical antitumor activity and non-cross-resistance in multidrug-resistant (MDR) tumor models" (Kuhl, Abstract).

11. Kuhl also discloses that "MMDX is activated in the liver to a >10 times more potent metabolite that cross-links DNA" (*id.*).

12. In addition, Kuhl discloses that "MMDX was approximately 3-100 times more active than DOX [(doxorubicin)], and [bioactivated MMDX] was 10-1,000 times more potent than DOX" (*id.*).

13. Specifically, Kuhl discloses that "MMDX and its bioactivated form . . . are highly active against [the tested] panel for human leukemia and lymphoma cell lines" (*id.*).

14. Additionally, Kuhl states that MMDX was dissolved in ethanol (*id.* at 11).

15. Nakamura discloses the "[e]ffects of lipiodol (LPD) on liver functions . . . in 130 patients with primary and metastatic liver cancer," as well as the effects of anticancer agent, Adriamycin (ADM) (Nakamura, Abstract).

16. Nakamura discloses that "the therapeutic effects of intraarterial infusion of ADM-LPD emulsion for advanced cancer . . . are remarkable" (*id.*).

17. It is undisputed that Adriamycin is the tradename for doxorubicin (Ans. 5; *see also* App. Br. 13).

18. Gorbunova discloses that, in the treatment of hepatic cancer, the "use of intrahepatic arterial infusion chemotherapy (IHAIC) techniques . . . allow[s] creating super high concentrations of an antitumor agent in the organ affected by the tumor and increasing frequency of the objectively recorded effects" (Gorbunova, Abstract).

PRINCIPLES OF LAW

"In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (1995) (internal quotations omitted). "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, ___, 127 S.Ct. 1727, 1742 (2007). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at ___, 127 S. Ct. at 1739.

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.

In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

"[O]bjective evidence of nonobviousness includes . . . unexpected results created by the claimed invention." *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). "It is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice." *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). In addition, *expected* beneficial results are not evidence of nonobviousness. *See In re Skoner*, 517 F.2d 947, 950 (CCPA 1975).

ANALYSIS

Nakamura discloses a composition for treating liver cancer comprising doxorubicin and lipiodol, which is an agent that remains selectively in a tumor after its injection through the hepatic artery (Findings of Fact (FF) 15-17 & 5). Kuhl discloses that MMDX, a methoxymorpholino derivative of doxorubicin, has a "broad spectrum of preclinical antitumor activity" (FF 10 & 2). Although Kuhl specifically relates to leukemia and lymphoma (FF 13), Bargiotti discloses that MMDX has also been shown to inhibit solid tumors (FF 6-9). We conclude that the Examiner has set forth a prima facie case that it would have been obvious to form a composition comprising MMDX and lipiodol. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l v. Teleflex Inc.*, 550 at ___, 127 S. Ct. at 1739. In addition, we conclude that the Examiner has set forth a prima facie case that it would have been obvious to use the resulting composition to treat liver cancer.

Furthermore, Gorbunova discloses the use of intrahepatic arterial infusion in the treatment of liver cancer (FF 18). Based on this teaching, we

also conclude that the Examiner has set forth a prima facie case that it would have been obvious to treat liver cancer by the intrahepatic administration of the MMDX-lipiodol composition.

With regard to claim 13, Appellants argue:

> Bargiotti . . . does not disclose or remotely suggest a pharmaceutical composition which includes MMDX and a pharmaceutically acceptable agent which remains selectively in a liver tumor after its injection. Moreover, this reference does not provide any teaching or suggestion of administrating an MMDX composition or indeed any morpholino derivative pharmaceutical composition within the scope of this reference into the hepatic artery.

(App. Br. 11.) Appellants also argue that Kuhl does not disclose "providing a MMDX composition with a pharmaceutically acceptable agent which remains selectively in a liver tumor after its injection through the hepatic artery" (*id.*). In fact, Appellants argue:

> The teaching of Kuhl et al. is away from Claim 13 . . . insofar as the Kuhl et al. disclosure of an MMDX composition is limited to the recitation of examples, at Page 11, in which MMDX is disclosed in a composition. That composition, however, combines MMDX with ethanol. That sole composition teaching is away from Claim[] 13 . . . because it is well known to those skilled in the art that such a composition, which is recited to be retained in the liver, will cause cirrhosis of the liver given the notorious biological effect of ethanol in effectuating such an outcome.

(*Id.* at 12.)

We are not persuaded. First, claim 13 does not require administrating an MMDX composition into the hepatic artery. Instead, claim 13 is directed to a composition comprising MMDX and a pharmaceutically acceptable

agent that has the property of remaining selectively in a liver tumor if it is injected through the hepatic artery.

Second, we do not agree that Kuhl teaches away from the composition of claim 13. As noted by the Examiner, Kuhl combines MMDX with ethanol (FF 14). Even if it would not have been obvious to combine the MMDX-ethanol combination with an agent that remains selectively in a liver tumor, we do not agree that Kuhl teaches away from combining MMDX with such an agent.

Third, the Examiner is not relying on Bargiotti or Kuhl to teach a composition comprising a pharmaceutically acceptable agent that remains selectively in a liver tumor. Instead, Nakamura is relied on for teaching this feature (Ans. 4).

In addition, Appellants argue that Nakamura does not teach or suggest MMDX (App Br. 12). However, because the Examiner is not relying on Nakamura to teach or suggest MMDX, we are not persuaded by this argument.

Appellants also argue that Nakamura "is not combinable with the principal Bargiotti et al. reference insofar as Bargiotti et al. is limited to morpholino derivatives of anthracyclines. DOX, the sole compound within the scope of Nakamura et al., is not a morpholino derivative of an anthracycline." (App. Br. 13.)

We are not persuaded. Nakamura discloses that the combination of doxorubicin and lipiodol had a remarkable therapeutic effect on advanced cancer (FF 16). Bargiotti, as well as Kuhl, discloses that MMDX, a derivative of doxorubicin, also has antitumor activity (FF 6-13 & 2). In fact,

Bargiotti and Kuhl both indicate that MMDX may actually be more effective that doxorubicin (FF 8 & 11-12). Thus, we agree with the Examiner that it would have been obvious to combine MMDX with lipiodol.

In addition, Appellants argue that Gorbunova "provides no weight, given its teaching of a chemically distinct compound" (App. Br. 13). The Examiner relies on Gorbunova for teaching intrahepatic administration of chemotherapy (Ans. 4). Given that claim 13 does not require intrahepatic administration, we conclude that this reference is not even needed to render claim 13 obvious.

Appellants also "observe that the optimum intravenous dose of MMDX is at least eighty times less than that of DOX" (Reply Br. 2-3). Appellants argue that this "dramatic difference in functionality of MMDX demonstrates far superior and unexpected efficacy over DOX, *in vivo*. This unexpected efficacy certainly would not have been appreciated by the skilled artisan at the time of the invention. As such, this remarkable efficacy rebuts any presumption of structural or functional obviousness." (*Id.* at 3.)

We are not persuaded. The Specification states that MMDX "differs from most anthracyclines in being highly potent when administered *in vivo*, the optimal i.v. dose being at least 80 fold less than that of doxorubicin" (FF 3). From the context of this statement, it is not clear whether the inventors intended this to be a statement of the prior art or a statement of an unexpected result, particularly since the focus of their invention appears to be the intrahepatic administration of MMDX rather than intravenous administration (FF 4). However, even if it was intended to be a statement of an unexpected result, given that Kuhl discloses that "MMDX was

approximately 3-100 times more active than DOX [(doxorubicin)], and [bioactivated MMDX] was 10-1,000 times more potent than DOX" (FF 12), we do not agree that this statement would be sufficient to rebut the prima facie case of obviousness.

With regard to claim 18, Appellants argue that "none of the applied references teach the administration of MMDX in the treatment of a human liver tumor wherein a therapeutic amount of that compound is intrahepatically administered to a patient in need thereof" (App. Br. 13).

In particular, Appellants argue that Bargiotti "merely discloses MMDX as a promising compound useful in providing antitumor activity in the treatment of murine tumors" (*id.* at 14). In addition, Appellants argue that Kuhl "merely discloses in vitro activity data suggesting that in tests of human leukemia and lymphoma cell lines MMDX was more sensitive than DOX" (*id.*). Appellants argue:

> Those skilled in the art are aware that such data as that provided in Kuhl et al. is not definitive of tumor specificity. That is, no disclosure is made in Kuhl et al. evidencing superior tumor reduction in any mammal. Indeed, the only teaching in Kuhl et al. is an in vitro showing of effectiveness against certain blood tumors. One skilled in the art would not thus be presented with a reasonable expectation of success upon using MMDX in the treatment of liver tumors.

(*Id.*) Appellants also argue that DeVita teaches that "agents useful in the treatment of blood tumors, such as leukemia and lymphoma, have no therapeutic efficacy against solid tumors" and therefore "further emphasizes the irrelevance of Kuhl. . . . Chemotherapeutic agents, such as MMDX, are tumor-specific and the results of chemotherapy depend on tumor growth characteristics and on the tumor's individual resistance to the drug." (*Id.* at

14-15.) Thus, Appellants argue that "the combined teaching of [Bargiotti and Kuhl] do not . . . suggest treatment of liver tumors by administration of MMDX, let alone intrahepatic introduction of that drug" (*id.* at 15).

We are not persuaded. We agree with Appellants that neither Bargiotti nor Kuhl specifically teach the treatment of liver cancer. However, given the fact that Kuhl describes MMDX as having "broad spectrum . . . antitumor activity" (FF 10), Bargiotti specifically discloses the inhibition of solid tumors (FF 9), and Nakamura discloses that a derivative of MMDX can be used to treat liver cancer (FF 15-17), we agree with the Examiner that there would have been a reasonable expectation for success. In particular, even assuming that DeVita generally teaches that "agents useful in the treatment of blood tumors, such as leukemia and lymphoma, have no therapeutic efficacy against solid tumors," Bargiotti teaches that MMDX inhibits solid tumors, specifically carcinomas (FF 9).

With regard to disclosing the intrahepatic administration of MMDX, the Examiner relies on Gorbunova (Ans. 4). Appellants have not adequately explained why it would not have been obvious to combine Gorbunova with the other references in order to suggest intrahepatic administration of MMDX.

In addition, Appellants argue:

> Kuhl et al. teaches that MMDX is activated in the liver to a highly active metabolite. This teaching . . . suggests that MMDX is transformed in the body into highly cytotoxic metabolites. Moreover, the Examiner admits that Gorbunova et al. teaches that intra-arterial infusion chemotherapy allows for the creation of extremely high concentrations of the antitumor agents in the organ affected by the tumor. Therefore, in view of the teachings from the prior art that extremely high

> concentrations of MMDX would be created around the liver by intrahepatic administration of MMDX, and MMDX would be transformed into highly cytotoxic metabolites, one skilled in the art would not have been motivated to even attempt to try to use MMDX in an intrahepatic administration for the treatment of liver tumors . . . , since such treatment would cause significant toxicity to the human body. Stated differently, the cited art provides a clear teaching away from the presently claimed invention.

(Reply Br. 4-5.)

We are not persuaded. The purpose of chemotherapy is to create a cytotoxic environment. Based on the noted teachings in Kuhl and Gorbunova, Appellants may have been motivated to use a lower amount of MMDX than doxorubicin or than would be used if MMDX was being administered by a route other than intrahepatic administration. However, we do not agree that the potential for significant toxicity would teach away from the method of claim 18.

With regard to claim 19, Appellants additionally argue that "even if there were a showing, by the combined teaching of the applied references, suggesting [treating liver cancer by the intrahepatic administration of MMDX], the showing of the unexpected result of reduced systemic exposure to MMDX, occasioned by its intrahepatic administration, rebuts any presumption of obviousness" (App. Br. 17). In particular, Appellants argue:

> The experimental protocol provided in the specification of the application on appeal establishes that a reduced concentration of MMDX, an admitted toxic compound, is required to treat liver cancer when administered intrahepatically through the hepatic artery. Thus, even if MMDX treatment of humans suffering from cancer were disclosed in the prior art, which is not the case, . . . its intrahepatic administration would still be

> patentable based on the unexpected result of reduced systemic exposure to the toxic chemotherapeutic agent, MMDX.

(*Id.*)

We are not persuaded. Gorbunova discloses that, in the treatment of hepatic cancer, the "use of intrahepatic arterial infusion chemotherapy (IHAIC) techniques . . . allow[s] creating super high concentrations of an antitumor agent in the organ affected by the tumor" (FF 18). Thus, we agree with the Examiner that, "[s]ince intra-arterial administration creates a high concentration in the organ affected by the tumor, one of skill in the art would expect reduced systemic exposure of the active agent . . . via intrahepatic arterial infusion" (Ans. 8). In particular, because intrahepatic administration creates a high concentration of antitumor agent at the site of the cancer, less overall antitumor agent would be required to achieve the same effect and therefore a reduced systemic exposure would be expected.

With regard to claims 24 and 25, Appellants argue that the "showing presented in the specification establish not only the effectiveness of the general method of treatment of human liver cancer but also at concentrations consistent with reduced systemic exposure to MMDX" (App. Br. 18). In particular, Appellants argue that claims 24 and 25 "provide specific treatment regimes . . . which provide . . . unexpectedly improved results" (*id.*).

We are not persuaded. In particular, for the reasons discussed above, we do not agree that Appellants have provided sufficient evidence of unexpected results for administering MMDX by intrahepatic administration, much less for the treatment regimes recited in claims 24 and 25.

With regard to claims 28-30,[4] Appellants argue that "the dosage range[s] set forth in [these claims], which is predicated upon both therapeutic effectiveness and minimizing of toxicity problems, would . . . be a patentable invention in view of the obtaining of these unexpected results" (App. Br. 19). However, we do not agree that Appellants have provided sufficient evidence of unexpected results for administering MMDX by intrahepatic administration, much less for the dosage ranges recited in claims 28-30.

With regard to claim 31, Appellants argue that it should "be appreciated that the requirement that the MMDX pharmaceutical composition remains selectively in the liver tumor after its injection through the hepatic artery is totally undisclosed in any of the applied references" (App. Br. 19). We are not persuaded. Claim 31 recites "a pharmaceutically acceptable agent which remains selectively in the liver tumor after its injection through the hepatic artery." Although Nakamura, at least in the English Abstract, does not recite that lipiodol is an "agent which remains selectively in the liver tumor after its injection through the hepatic artery," the Specification discloses that it is such an agent (FF 5). Thus, based on the disclosure in Nakamura, we agree with the Examiner that it would have been obvious to administer lipiodol, together with an antitumor agent, to treat a human liver tumor.

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[4] It is noted that claims 28-30 depend from claim 1, which is no longer pending in this application.

CONCLUSION

The Examiner has set forth a prima facie case that: (a) it would have been obvious to combine MMDX with lipiodol; and (b) it would have been obvious to treat liver cancer by the intrahepatic administration of MMDX. In addition, Appellants have not provided sufficient evidence of unexpected results to overcome the Examiner's prima facie case of obviousness.

We therefore affirm the rejection of claims 13, 18, 19, 24, 25, and 28-31. Claim 14 and claims 20-23, 26, and 27 have been argued with claims 13 and 18, respectively, and therefore fall with claims 13 and 18. 37 C.F.R. § 41.37(c)(1)(vii).

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

LP

PETER I. BERNSTEIN
BERNSTEIN, SCULLY, SCOTT, MURPHY & PRESSER
400 GARDEN CITY PLAZA
GARDEN CITY NY 11530